Review Article

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Molecular mechanisms of cellular aging: A systems physiology perspective

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ABSTRACT

Cellular aging is a complex biological process characterized by a gradual decline in the ability of cells to maintain homeostasis, respond to stress, and sustain tissue function. This phenomenon is driven by the accumulation of interacting molecular and physiological changes, ultimately contributing to impaired organ function and increased susceptibility to age-related diseases. Although reductionist approaches have revealed key pathways and molecules involved in aging, they have not fully explained the dynamics of interactions across levels of biological organization that make aging a systemic phenomenon. This review aimed to integrate the molecular mechanisms of cellular aging within the framework of systems physiology, emphasizing the interconnectedness of molecular changes, cell function, and physiological regulation at the tissue and organism levels. The literature was obtained through a search of major scientific databases with a focus on experimental and computational studies addressing cellular aging, hallmarks of aging, and systems and multi-omics approaches. The synthesis of results demonstrates that key mechanisms of aging—such as genomic instability, mitochondrial dysfunction, impaired proteostasis, deregulated nutrient sensing, cellular senescence, and altered intercellular communication—form a dynamic and interconnected regulatory network. The nonlinear interactions between these pathways explain variations in aging across tissues and individuals, while emphasizing the importance of physiological context in determining biological outcomes. A systems physiology approach provides a more comprehensive understanding of how changes at the molecular level translate into systemic decline. Overall, a systems-based perspective offers a robust conceptual framework for integrating molecular findings on aging and supporting the development of more effective, predictive, and physiologically relevant intervention strategies to maintain health across the lifespan.

Introduction

Biological aging is a natural phenomenon characterized by a progressive decline in an organism's ability to maintain internal balance and cope with physiological stress (Maldonado *et al*., 2023). At the cellular level, this process is characterized by the accumulation of molecular and functional changes over time, such as reduced proliferative capacity, impaired metabolic regulation, and decreased effectiveness of cellular repair systems (Li *et al*., 2024). Cellular aging is not solely driven by intrinsic factors—such as DNA damage and mitochondrial dysfunction—but is also influenced by extrinsic factors, including signals from the tissue microenvironment and regulation originating from the organism's overall systems (López-Otín *et al*., 2023).

The significance of cellular aging is becoming increasingly apparent with the increasing incidence of age-related degenerative diseases (Gerdes *et al*., 2020). A wide range of pathological disorders—such as cardiovascular, neurodegenerative, metabolic, and cancer—show a strong link to the biological changes that accompany the aging process (Li *et al*., 2021). In many situations, cellular aging contributes to tissue function decline through reduced regenerative capacity, increased chronic low-grade inflammation, and impaired intercellular communication (López-Otín *et al*., 2013). Therefore, aging is no longer understood simply as a chronological phenomenon, but rather as a fundamental biological factor that determines health and physiological function throughout the lifespan (Cohen *et al*., 2020).

To explain the complexity of aging, the concept of hallmarks of aging was introduced as a conceptual framework that groups the main molecular mechanisms underlying the aging process (Tartiere *et al*., 2024). This framework encompasses several essential characteristics, including genomic instability, telomere shortening, epigenetic changes, impaired proteostasis, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication (Tenchov *et al*., 2024a). As research progresses, the concept of hallmarks of aging has evolved conceptually, no longer viewed as a collection of stand-alone mechanisms, but rather as a network of interconnected biological processes that dynamically interact with one another (Kiseleva *et al*., 2024).

While the hallmarks-based approach has provided a strong foundation for understanding the biology of aging, deepening this concept requires a perspective that goes beyond the analysis of a single molecular pathway in isolation (Slade *et al*., 2024). Aging results from the nonlinear interaction of multiple interconnected biological pathways across levels of organization, from molecules to entire physiological systems (Shen *et al*., 2024). Within this framework, the systems physiology approach is increasingly important, viewing aging as an emergent phenomenon arising from the integrated function of cells, tissues, organs, and body systems (Cohen *et al*., 2022). This perspective allows for exploration of how changes at the molecular level can be amplified, modified, or even compensated for by the broader physiological context.

Systems physiology highlights the crucial role of regulatory networks, feedback mechanisms, and communication between biological systems in shaping aging trajectories (Asejeje and Ogunro, 2024). This approach goes beyond identifying key molecules and assesses their functional consequences on the organism's internal balance (Guo *et al*., 2022). By integrating multi-omics data, cellular dynamics, and physiological parameters, systems physiology provides a more comprehensive analytical framework for explaining the heterogeneity of aging processes and differences in biological responses between individuals (Kiseleva *et al*.,

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2024).

Based on this description, this review aimed to analyze the molecular mechanisms of cellular aging from a systems physiology perspective. This article examined the interrelationships between aging pathways and their contribution to physiological disorders at the tissue and body system levels. Furthermore, it discussed the implications of an integrative approach for identifying intervention targets and designing more optimal therapeutic strategies. With this approach, this article is expected to provide a more comprehensive understanding of the aging process and encourage the development of systems-based aging research in the future.

Conceptual framework: cellular aging in systems physiology

Cellular aging cannot be fully understood as the result of isolated molecular changes, but rather as an emergent phenomenon that arises from dynamic interactions between biological components at multiple levels of organization.

Definition and scope of systems physiology

Systems physiology is an integrative approach to physiology that emphasizes understanding biological function as a result of dynamic interactions between components at various levels of organization, from molecules to the entire organism (Billman, 2020). Unlike reductionist approaches that examine single pathways or molecules in isolation, systems physiology views physiological phenomena as the product of interconnected, nonlinear regulatory networks governed by complex feedback mechanisms (Parker, 2022). Within this framework, changes in a single molecular element can elicit adaptive or maladaptive responses at the cellular, tissue, and organ levels (Long *et al*., 2025).

In the context of cellular aging, systems physiology offers a conceptual framework for understanding how the accumulation of molecular perturbations—such as genomic instability, mitochondrial dysfunction, and metabolic deregulation—not only affects individual cells but also disrupts the balance of tissue and systemic function in the organism (Amorim *et al*., 2022). These interactions across levels of organization create opportunities for amplification of aging signals, allowing relatively small changes in molecular regulation to translate into significant physiological decline at the organ and system levels (Khan *et al*., 2017).

The scope of systems physiology in the study of aging encompasses the integration of multiple biological systems—such as the metabolic, immune, endocrine, and nervous systems—that collectively shape adaptive responses to stress and environmental changes throughout life (van den Beld *et al*., 2018). This approach allows for the identification of common patterns and intersections among aging pathways, leading to a more comprehensive understanding of the fundamental mechanisms of aging (Asejeje and Ogunro, 2024). Furthermore, this framework opens the door to designing intervention strategies that target regulatory networks in an integrated manner, rather than focusing on a single molecule or pathway.

Integration of molecular networks in aging

Cellular aging is a consequence of gradual changes in molecular regulatory networks involving complex interactions between genes, proteins, and metabolites (Zhao *et al*., 2024). These networks do not operate in a linear or isolated manner, but rather form an integrated system that regulates the cell's response to stress, energy demands, and various environmental signals (An *et al*., 2025). As aging progresses, small disturbances in any one component—for example, changes in gene expression or enzyme activity—can affect the stability of the entire system through signal propagation mechanisms between interconnected pathways (Tenchov *et al*., 2024a).

The integration of transcriptional, proteomic, and metabolic networks plays a key role in shaping the course and dynamics of cellular aging (Hoffman *et al*., 2017). Alterations in gene regulation can alter the composition and function of expressed proteins, which in turn impacts the flow of metabolites and the cell's bioenergetic balance (Carthew, 2021). This disharmony is often exacerbated by a decline in the cell's adaptive ability to adjust the activity of its biological network, resulting in cumulative dysfunction and ultimately contributing to the disruption of cellular and tissue homeostasis (Hornisch and Piazza, 2025).

One of the key characteristics of molecular networks in aging is their nonlinear nature, so that cause-and-effect relationships are not proportional and are often mediated by feedback mechanisms, both positive and negative (Kriete *et al*., 2010). These feedback mechanisms can serve a protective function by maintaining cellular stability, but under conditions of chronic stress or accumulated damage, the same responses can potentially accelerate cellular dysfunction (Cohen, 2016). Furthermore, biological redundancy—which normally provides resilience to single insults—tends to diminish with age. As a result, regulatory networks become increasingly vulnerable to malfunction (Walker, 2022).

Within the framework of systems physiology, the integration of molecular networks during aging demonstrates that aging is not simply a random accumulation of damage, but rather a consequence of dynamic reorganization within biological systems (Cohen *et al*., 2022). Therefore, understanding the patterns of interactions, convergence, and interdependencies between pathways is crucial for identifying intervention targets that can more optimally modulate the entire aging network, compared to strategies that target only a single molecule or pathway.

Core molecular hallmarks of cellular aging

Cellular aging is characterized by a series of fundamental molecular changes that progressively disrupt genomic stability, metabolic regulation, and the integrity of cellular function. Table 1 summarizes the

Table 1. Core molecular hallmarks of cellular aging and their systems-level implications.

Molecular hallmark	Core mechanism	Cellular impact	Tissue and systems-level implications
Genomic instability and DNA damage response (DDR)	Accumulation of DNA damage, activation of ATM/ATR and p53, and decreased DNA repair efficiency	Persistent mutations, cell cycle arrest, and senescence or apoptosis	Chronic tissue inflammation, disrupted homeostasis, and reduced systemic function
Telomere attrition and replicative senescence	Progressive telomere shortening, shelterin dysfunction, and activation of DNA damage response	Loss of proliferative capacity and cell division arrest	Impaired tissue regeneration and accumulation of senescent cells
Epigenetic alterations	Global DNA hypomethylation, focal hypermethylation, histone modification changes, and epigenetic drift	Gene expression dysregulation and loss of cell identity stability	Functional heterogeneity and impaired tissue coordination
Loss of proteostasis	Chaperone dysfunction and decreased ubiquitin–proteasome activity and autophagy	Accumulation of misfolded proteins and toxic aggregates	Chronic cellular stress, tissue, and organ dysfunction
Mitochondrial dysfunction and oxidative stress	Reduced oxidative phosphorylation, increased ROS, and impaired retrograde signaling	Bioenergetic deficits, macromolecular damage	Decline in high-energy tissues (brain, muscle, and heart)
Deregulated nutrient sensing	Chronic activation of insulin/IGF-1 and mTOR, reduced AMPK and sirtuin activity	Imbalance between anabolism and cellular maintenance	Accelerated systemic aging and reduced metabolic flexibility

key molecular hallmarks of cellular aging, along with their biological mechanisms, consequences at the cellular level, and implications for the function of tissues and organismal systems. Figure 1 presents the core molecular hallmarks of cellular aging, illustrating the fundamental biological alterations that progressively disrupt genomic stability, metabolic homeostasis, and cellular functional integrity.

Genomic instability and DNA damage response

Genome instability is a key characteristic of cellular aging, characterized by the accumulation of Deoxyribonucleic Acid (DNA) damage due to exposure to various internal and external stressors over time (Burhans and Weinberger, 2007). Sources of this damage include replication errors, increased oxidative stress, and changes in chromatin structure, which gradually increase the incidence of mutations and chromosomal abnormalities (Vijg and Montagna, 2017). When the level of damage exceeds the capacity of the cell's repair system, genome integrity is compromised, triggering both permanent and progressive changes in cell function (López-Gil *et al*., 2023).

The DNA damage response (DDR) serves as a molecular surveillance mechanism that maintains genome stability through the detection of DNA lesions, cell cycle arrest, and activation of repair systems (Cui *et al*., 2025). The protein kinases Ataxia Telangiectasia Mutated (ATM) and ATM and Rad3-related (ATR) act as primary sensors that recognize DNA breaks and replication stress, then trigger a phosphorylation cascade that activates various downstream effectors (Helt *et al*., 2005). Through activation of these pathways, cells can determine the appropriate physiological response, ranging from repairing damaged DNA to inducing senescence or apoptosis when the level of damage is beyond repair (Chen *et al*., 2007).

The transcription factor protein 53 kilodalton (p53) plays a key role in integrating DDR signals with cell fate determination (Tomas *et al*., 2024). By regulating the expression of genes that control cell cycle arrest, DNA repair, and programmed death, p53 acts as a link between maintaining genomic stability and balanced tissue function (Chen, 2016). However, with aging, the effectiveness of this pathway tends to decline due to disruption of damage sensors, reduced repair system capacity, and changes in epigenetic regulation. This ultimately increases cell tolerance to persistent genomic damage (An *et al*., 2025).

From a systems physiology perspective, genomic instability and DDR mechanisms not only have consequences at the individual cell level but also impact the function of tissues and organismal systems as a whole (Alhmoud *et al*., 2020). Cells experiencing chronic DNA damage can enter a state of senescence and release proinflammatory signals that affect their surrounding environment, thus extending the effects of genomic instability to the tissue level (Roger *et al*., 2021). Thus, genomic aging can be viewed as a failure of an integrated molecular surveillance system, where weakened coordination among DDR pathways contributes to the systemic decline of physiological function (Wang *et al*., 2025a).

Telomere attrition and replicative senescence

Telomeres are specialized nucleoprotein structures located at the ends of chromosomes and play a role in protecting DNA from degradation and interchromosomal fusion (Alanazi *et al*., 2024). With each round of replication, telomeres gradually shorten due to limitations in the DNA replication mechanism at the chromosome terminals (Muraki *et al*., 2012). This shortening process is influenced by the activity of the telomerase enzyme, the cell's oxidative state, and the stability of the shelterin complex, which maintains the integrity of the telomere structure (von Zglinicki, 2002). Discordance among these factors can accelerate telomere length loss and increase the risk of genomic dysfunction (Chen *et al*., 2026).

When telomere shortening reaches a critical point, cells recognize this as a signal of DNA damage and trigger a protective response that halts proliferation (Lin and Epel, 2022). This phenomenon is known as replicative senescence and reflects a biological mechanism that limits the ability of normal cell division (Hemann *et al*., 2001). This limit to proliferation, classically referred to as the Hayflick limit, plays a crucial role in preventing genomic instability from excessive replication (de Bardet *et al*., 2023). However, this mechanism also contributes to the decline in tissue regenerative capacity with aging (Clayton and Shadel, 2014).

At the systemic physiological level, the accumulation of cells entering replicative senescence has a significant impact on tissue balance (Burton and Krizhanovsky, 2014). These cells are no longer able to contribute to repair and regeneration processes and can modify the microenvironment through the release of bioactive mediators that affect surrounding cells (Kumari and Jat, 2021). Thus, telomere shortening represents more than just a marker of cellular biological time, but also serves as a link between molecular changes and tissue functional decline (Baylie *et al*., 2026).

Within the framework of systems physiology, telomere attrition and replicative senescence are viewed as components of a more comprehensive aging regulatory network (Di Micco *et al*., 2021). The interplay between telomere length, DNA damage response pathways, and metabolic

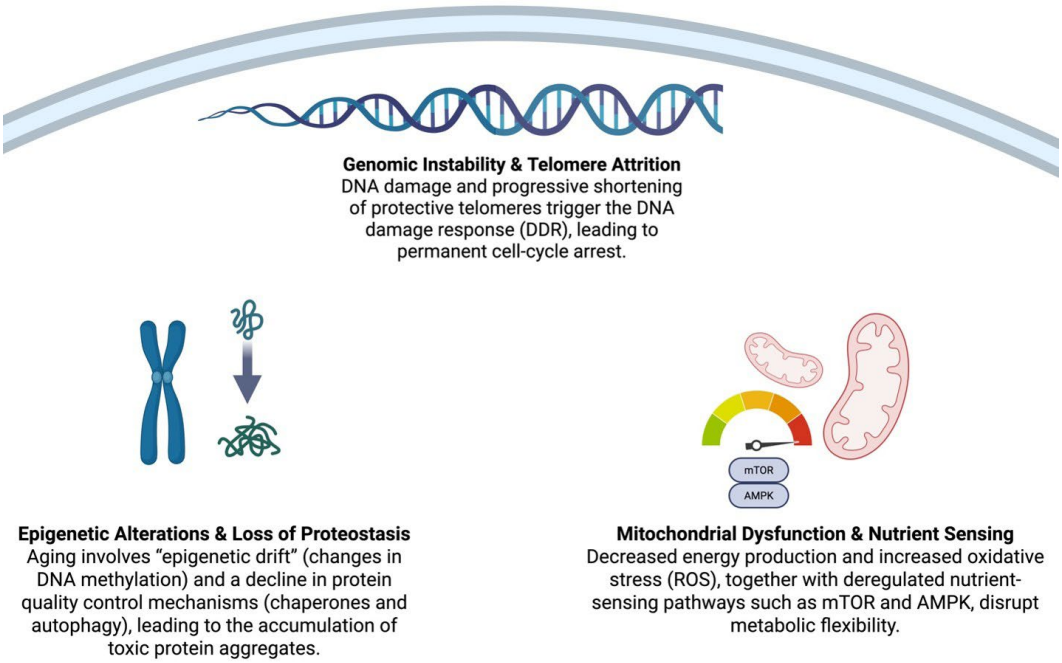

Figure 1. The core molecular hallmarks of aging

signaling plays a role in determining the balance between protecting genome integrity and maintaining cell proliferation (Torres-Montaner, 2023). Disruption of coordination between these pathways can accelerate the shift from a protective adaptive response to a state of cellular and systemic dysfunction, ultimately contributing to the emergence of an aging phenotype at the organismal level (Huang *et al*., 2025).

Epigenetic alterations

Epigenetic changes are a crucial mechanism linking genetic, environmental, and cellular aging factors without altering the DNA nucleotide sequence (López-Gil *et al*., 2023). Throughout the aging process, the epigenetic landscape undergoes gradual reorganization, affecting the regulation of gene expression, the stability of cell identity, and the ability to adapt to stress (An *et al*., 2025). These changes are accumulative and contribute to the increasing heterogeneity of cell function in aging tissues (Wang *et al*., 2022).

One of the main characteristics of epigenetic aging is a shift in DNA methylation patterns, characterized by global hypomethylation and specific hypermethylation in the promoter regions of certain genes (Vaidya *et al*., 2025). A decrease in overall methylation can trigger genomic instability and disrupt transcriptional regulation, while increased methylation in genes involved in DNA repair, differentiation, and cell cycle control can inhibit cellular protective mechanisms (Sriraman *et al*., 2020). This pattern of disharmony reflects a decline in the precision and stability of the epigenetic regulatory system with aging (Rembiałkowska *et al*., 2025).

In addition to changes in DNA methylation, histone modifications and chromatin remodeling processes also contribute significantly to cellular aging (Lossi *et al*., 2024). Variations in histone acetylation, methylation, and phosphorylation patterns influence the degree of chromatin openness to transcription complexes, thus broadly impacting the regulation of gene expression (Bannister and Kouzarides, 2011). With aging, chromatin structure tends to shift from a well-organized state to a looser or less stable one (Margueron and Reinberg, 2010). These changes affect the consistency of gene regulation and the cell's ability to respond appropriately to physiological signals (Dong and Weng, 2013).

The phenomenon of epigenetic drift refers to the gradual, random emergence of epigenetic variations among genetically identical cells (Fan *et al*., 2025). This process increases epigenetic heterogeneity within a tissue, which can ultimately disrupt the synchronization of cell function at the tissue and organ levels (Pisaruk, 2025). From a systems physiology perspective, epigenetic changes cannot be considered as isolated events, but rather as part of a broader reorganization of molecular regulatory networks (Corso-Díaz *et al*., 2018). This epigenetic instability weakens the integration of biological pathways and accelerates the shift toward physiological dysfunction that is a key characteristic of systemic aging (Faraji and Metz, 2026).

Loss of proteostasis

Proteostasis is the cell's ability to maintain a balance between protein synthesis, folding, repair, and degradation to ensure optimal cell function (Shukla and Narayan, 2025). This mechanism relies on the integrated coordination of molecular chaperones, protein degradation systems, and intracellular quality control pathways (Díaz-Villanueva *et al*., 2015). With aging, proteostasis capacity gradually declines, leading to the accumulation of misfolded proteins and toxic protein aggregates within cells (Hipp *et al*., 2019).

Impaired protein chaperone function is a major factor triggering proteostasis imbalances in the aging process (Acquarone *et al*., 2025). Chaperones, including those belonging to the heat shock proteins (HSPs), play a role in assisting the folding of newly synthesized proteins and preventing inappropriate protein interactions (Turturici *et al*., 2011). In aging cells, chaperone expression and activity generally decline, preventing proteins experiencing conformational stress from being optimally repaired (Tan *et al*., 2020). Consequently, dysfunctional proteins can escape quality control mechanisms and disrupt essential cellular pathways (Ye *et al*., 2025).

In addition to chaperone dysfunction, impaired ubiquitin-proteasome function also contributes to the increased accumulation of abnormal proteins (Hartl and Hayer-Hartl, 2009). This system functions by marking damaged proteins with ubiquitin molecules and directing them to the degradation pathway via the proteasome (Höhn *et al*., 2020). With aging, proteasome activity tends to decline and the precision of degradation selection becomes less precise, resulting in dysfunctional proteins persisting longer within the cell (Saez and Vilchez, 2014). This situation is further exacerbated by a decline in autophagy capacity, particularly macroautophagy, which plays a crucial role in clearing large protein aggregates and damaged organelles (Zhang *et al*., 2022).

Within the framework of systems physiology, decreased proteostasis not only affects individual cell stability but also impacts tissue function due to disrupted coordination between cellular protective pathways (Hipp and Hartl, 2024). The accumulation of dysfunctional proteins triggers prolonged cellular stress, shifts the regulation of metabolic and inflammatory signals, and accelerates the cell's transition to senescence, or programmed death (Xie *et al*., 2025). Therefore, impaired proteostasis can be viewed as the intersection of various aging mechanisms that collectively undermine physiological stability at the systemic level (Morimoto and Cuervo, 2014).

Mitochondrial dysfunction and oxidative stress

Mitochondria play a key role in maintaining cellular homeostasis through energy production, metabolic regulation, and modulation of cell death signals (Wang *et al*., 2025b). With aging, mitochondrial function gradually declines, characterized by decreased oxidative phosphorylation efficiency, altered balance between fusion and fission dynamics, and increased accumulation of mutations in mitochondrial DNA (Chistiakov *et al*., 2014). This dysfunction directly impacts the cell's bioenergetic capacity and reduces its ability to adapt to changing physiological demands over time (Mone *et al*., 2024).

Decreased electron transport chain performance leads to increased electron leakage, ultimately accelerating the formation of reactive oxygen species (ROS) (Zhao *et al*., 2019). Under normal circumstances, ROS act as signaling molecules that regulate differentiation, proliferation, and stress responses (Schieber and Chandel, 2014). However, in aging cells, the balance between ROS production and the antioxidant system is disrupted, transforming ROS from adaptive mediators into molecularly damaging agents (Poljsak *et al*., 2013). The accumulation of oxidative stress damages lipids, proteins, and nucleic acids, further exacerbating mitochondrial dysfunction through detrimental feedback mechanisms (Cojocaru *et al*., 2023).

In addition to causing direct damage, mitochondrial dysfunction also modulates other aging pathways through changes in metabolite profiles and redox signaling balance (Xu *et al*., 2025). Decreased NAD^+/NADH ratios, shifts in protein acetylation patterns, and disruption of communication between mitochondria and the nucleus (mitochondrial retrograde signaling) can alter gene expression regulation and cellular responses to stress (Amjad *et al*., 2021). This confirms that mitochondria serve not only as energy producers but also as signal integration centers that influence cell fate throughout the aging process (Zhang *et al*., 2018).

Within the framework of systems physiology, mitochondrial dysfunction and increased oxidative stress reflect a mechanism of aging that has widespread systemic impacts (Cui *et al*., 2012). Bioenergetic disturbances at the cellular level can lead to decreased performance in tissues with high energy demands, such as muscle, brain, and heart (Kuznetsov *et al*., 2025). Furthermore, prooxidative signals and metabolic changes released by cells with compromised mitochondria can affect neighboring cells, extending the effects of aging to the tissue and organ levels (Di Meo *et al*.,

2016). Therefore, mitochondrial aging reflects a weakening of the coordination between energy production, redox balance, and communication between integrated physiological pathways (Yin *et al*., 2016).

Deregulated nutrient sensing

The ability of cells to detect and respond to nutrient availability is a fundamental mechanism for maintaining the balance between growth, maintenance, and survival (Yuan *et al*., 2013). Nutrient-sensing pathways act as a bridge between metabolic states and molecular regulation, allowing cells to adjust their physiological activities according to environmental changes (Efeyan *et al*., 2015). With aging, the precision of these pathways tends to decline, ultimately leading to an imbalance between anabolic signals and cellular protective mechanisms (Horlem *et al*., 2025).

The insulin and insulin-like growth factor-1 (IGF-1) pathways play key roles in regulating growth and energy metabolism (Yakar and Adamo, 2012). Chronic activation of these pathways under conditions of nutrient excess stimulates proliferation and protein synthesis, but can also suppress cellular repair mechanisms and stress responses (Macvanin *et al*., 2023). In aging organisms, increased sensitivity to or prolonged exposure to insulin/IGF-1 signaling can accelerate cellular aging through increased oxidative stress, impaired mitochondrial function, and decreased proteostatic capacity (Lee and Lee, 2022).

Mammalian target of rapamycin (mTOR) functions as a central integration site for signals related to nutrient availability, energy status, and growth factors (Jesus *et al*., 2017). Persistently increased mTOR activity during aging drives cells into a sustained anabolic state, suppressing autophagy and facilitating the accumulation of damaged cellular components (Cayo *et al*., 2021). Conversely, AMP-activated protein kinase (AMPK) acts as an energy sensor, activated during energy deficits and directing cells along maintenance pathways, including increased substrate oxidation and stimulation of autophagy (Hardie, 2011). Reduced AMPK sensitivity or responsiveness in aging cells reduces metabolic flexibility and exacerbates cellular energy imbalance (Garcia and Shaw, 2017).

Sirtuins, particularly those dependent on NAD^+, act as epigenetic and metabolic regulators that coordinate cellular responses to nutrient availability and stress (Ji *et al*., 2025). With aging, decreased NAD^+ levels limit sirtuin activity, disrupting gene expression regulation, mitochondrial function, and cellular repair mechanisms (Imai and Guarente, 2014). Imbalances between the mTOR, AMPK, and sirtuin pathways reflect deregulation of an integrated nutrient-sensing network, not simply a disruption of one pathway in isolation (Sadria and Layton, 2021).

From a systems physiology perspective, disruption of nutrient sensing systems illustrates how changes in metabolic signaling at the molecular level can have broad impacts on the function of tissues and body systems as a whole (Smith *et al*., 2018). Asynchronization between the insulin/IGF-1, mTOR, AMPK, and sirtuin pathways undermines the balance between cell growth and maintenance, accelerating the emergence of systemic aging phenotypes (Sadria and Layton, 2021). Therefore, approaches that target the integrated modulation of nutrient sensing networks are crucial strategies for understanding and potentially slowing the rate of biological aging.

Cellular senescence as a system-level phenomenon

Cellular senescence is a complex biological response that not only affects individual cells but also shapes the dynamics of tissue function and physiological systems through paracrine interactions and cross-scale regulation. Figure 2 illustrates the transition from cellular senescence as an intrinsic cellular program to a broader system-level phenomenon that contributes to tissue dysfunction.

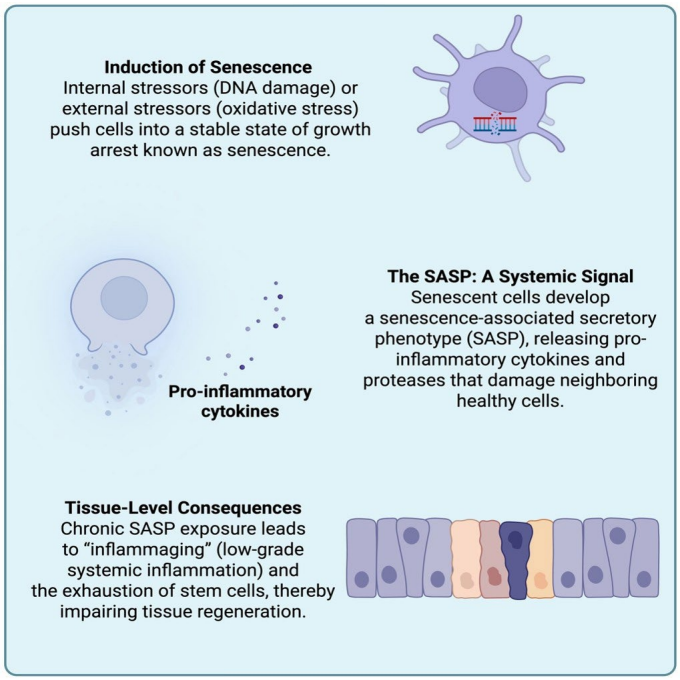

Figure 2. The Transition from cellular senescence to tissue dysfunction.

Mechanisms of senescence induction

Cellular senescence is a stable state of cell cycle arrest triggered in response to a variety of stresses, both internal and external (Herranz and Gil, 2018). Its induction process does not follow a single mechanism, but rather reflects different biological pathways depending on the type and severity of stress experienced (Liao *et al*., 2021). The two most widely studied forms are replicative senescence and stress-induced premature senescence (SIPS) (Rajarajacholan and Riabowol, 2015). Although both produce relatively similar final phenotypes, each is activated by distinct triggers and molecular dynamics (Dierick *et al*., 2002).

Replicative senescence primarily occurs due to the gradual shortening of telomeres as a consequence of repeated cell division (Victorelli and Passos, 2017). When telomere length reaches a critical threshold, chromosome ends lose their protective function and are identified as a form of DNA damage (Cleal *et al*., 2018). This situation triggers the activation of the DNA damage response pathway involving ATM/ATR and p53, which then leads the cell to permanent cell cycle arrest (Reinhardt *et al*., 2007). This mechanism acts as a physiological safeguard to prevent genomic instability from unrestricted replication (Cheng and Chen, 2010). However, on the other hand, this process also limits the proliferative capacity of somatic cells and contributes to the decline in tissue regeneration during aging (Yun, 2015).

In contrast, stress-induced senescence can occur independently of telomere length and is triggered by various forms of non-replicative stress, such as oxidative stress, mitochondrial dysfunction, oncogene activation, acute DNA damage, and proteostasis imbalance (Qin *et al*., 2024). In these conditions, excessive or prolonged exposure to stress activates the p16INK4a–RB and/or p53–p21 pathways, causing cells to enter cell cycle arrest even though their replicative capacity has not yet been fully achieved (Feng *et al*., 2025). SIPS represents an adaptive response to an adverse environment. However, if cells in this state accumulate, it can accelerate tissue deterioration (Ozdemir *et al*., 2025).

Within the framework of systems physiology, the distinction between replicative senescence and stress-induced senescence is not solely determined by the triggering factors, but also by their impact on the biological system as a whole (Dodig *et al*., 2019). Replicative senescence is progressive and generally parallels chronological aging (Wagner *et al*., 2009). Conversely, stress-induced senescence can occur earlier and exhibits a non-uniform distribution across tissues, depending on the intensity of stress exposure and the underlying physiological conditions (Reimann

et al., 2024). The dynamic interaction between these two mechanisms results in a heterogeneous pattern of tissue senescence, where the accumulation of senescent cells represents an integration of the cell's replicative history, accumulated stress load, and the adaptive capacity of the biological system (Li *et al*., 2024).

Senescence-Associated Secretory Phenotype (SASP)

Senescence-associated secretory phenotype (SASP) describes the complex secretory pattern produced by senescent cells, encompassing a variety of proinflammatory cytokines, chemokines, growth factors, proteases, lipid mediators, and extracellular matrix components (Alam *et al*., 2025). Unlike transient physiological secretions, SASP is persistent and reflects fundamental changes in the senescent cell's transcriptional program (Klepacki *et al*., 2025). The composition of SASP is heterogeneous, strongly influenced by cell type, senescence trigger, and the tissue context in which the cells reside (Alqahtani *et al*., 2025).

SASP regulation is controlled through the integration of multiple key signaling pathways, including chronic activation of the DNA damage response, oxidative stress, and impaired mitochondrial function (Klepacki *et al*., 2025). Transcription factors such as Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and CCAAT/Enhancer-Binding Protein beta (C/EBPβ) play central roles in regulating SASP gene expression, while the p38 MAPK and mTOR pathways modulate the strength and stability of the secretory response (Kumari and Jat, 2021). Furthermore, metabolic and epigenetic changes in senescent cells shape the SASP profile by influencing energy availability, chromatin accessibility, and protein translation efficiency (Cuollo *et al*., 2020). This multilevel regulation emphasizes that SASP is a systemic output of an interconnected signaling network, not simply a passive consequence of cell cycle arrest (Krupa *et al*., 2026).

At the tissue level, SASP exhibits ambivalent effects depending on the physiological context (Giroud *et al*., 2023). Under short-term or acute conditions, SASP mediators can support tissue repair and the elimination of damaged cells through immune system activation (Kale *et al*., 2020). However, with aging, the accumulation of senescent cells leads to chronic SASP exposure, disrupting tissue homeostasis (Kuehnemann and Wiley, 2024). A microenvironment rich in proinflammatory and proteolytic mediators can trigger dysfunction of surrounding cells, promote secondary senescence, and inhibit stem cell differentiation and function (Vernot, 2020). Thus, SASP is a key driver of persistent low-grade inflammation and decreased tissue regenerative capacity (Klepacki *et al*., 2025).

Within the framework of systems physiology, the SASP serves as an intercellular communication mechanism that extends the effects of senescence beyond the boundaries of individual cells (Cuollo *et al*., 2020). Signals released by senescent cells can spread both locally and systemically, influencing organ function and interactions between physiological systems, including the immune, metabolic, and endocrine systems (Khosla *et al*., 2020). Thus, the SASP serves as a meeting point between molecular changes in senescent cells and the tissue dysfunction that characterizes aging organisms (Venkataraman *et al*., 2024). A thorough understanding of the regulation and systemic impact of the SASP is crucial for designing intervention strategies that target pathological communication without compromising the contextually protective role of senescence.

Physiological and pathological roles of senescent cells

Senescent cells are not simply cells that have lost their function, but also reflect a biological state with multiple roles that are strongly influenced by physiological context and time (Herranz and Gil, 2018). From an adaptive perspective, senescence serves as a protective mechanism that maintains tissue integrity by halting the proliferation of cells that experience damage or excessive stress (Qin *et al*., 2025). This response prevents the spread of genomic instability and plays a role in controlling tumor growth, making senescence a crucial component of the organism's defense system (Ozdemir *et al*., 2025).

In the acute or controlled phase, senescent cells also play a role in normal physiological processes, such as embryonic development and tissue repair (Saito *et al*., 2024). Through the secretion of various mediators, these cells can modify the tissue microenvironment, promote extracellular matrix remodeling, and recruit immune cells to eliminate damaged cells (Liu *et al*., 2025a). Under these conditions, senescence is transient and coordinated, with the immune system's elimination of senescent cells as the final step, restoring tissue homeostasis (Tominaga, 2015).

Conversely, senescence becomes maladaptive when senescent cells are not successfully eliminated and accumulate with age or exposure to chronic stress (Huang *et al*., 2022). This accumulation transforms senescence's protective role into a source of tissue dysfunction (McHugh and Gil, 2018). Surviving senescent cells maintain secretory activity that can disrupt the function of neighboring cells, inhibit regeneration processes, and amplify chronic low-grade inflammation (Wu *et al*., 2025). These cumulative effects accelerate organ decline and increase susceptibility to age-related diseases, including metabolic disorders, fibrosis, and tissue degeneration (Kirichenko *et al*., 2025).

Within the framework of systems physiology, the shift of senescence from an adaptive to a maladaptive state reflects a failure of coordination between biological systems, particularly between somatic cells, the immune system, and the tissue microenvironment (Chen *et al*., 2025a). This imbalance suggests that the effects of senescence depend not only on the presence of senescent cells themselves, but also on the dynamics of their interactions and the ability of the organism's systems to control and eliminate them (Kumari and Jat, 2021). Therefore, understanding the dual role of senescent cells is crucial for interpreting aging as a systemic process and designing intervention strategies that maintain the physiological benefits of senescence while minimizing its pathological impact.

Table 2. Changes in intercellular communication and their consequences for tissue aging.

Major process	Biological feature	Key mechanism	Tissue and systems-level impact
Inflammaging	Persistent low-grade chronic inflammation during aging	Constitutive activation of proinflammatory cytokines and failure of inflammation resolution	Disrupted tissue homeostasis and increased risk of age-related diseases
Immune dysregulation	Reduced precision of immune responses and increased non-specific basal activity	Chronic antigen exposure and accumulation of molecular damage	Shift of immune function from protective to systemic proinflammatory
Immune–somatic cell interaction	Bidirectional communication forming inflammatory feedback loops	Release of danger signals by stressed/senescent cells and immune cytokines	Maintenance of chronic inflammation and reduced regenerative capacity
Stem cell exhaustion	Decline in proliferation, differentiation, and self-renewal of stem cells	Senescence, apoptosis, and intrinsic stem cell damage	Limited tissue regeneration and decreased organ function
Stem cell niche disruption	Altered microenvironment supporting stem cells	Extracellular matrix alterations, inflammation, reduced vascularization	Improper activation or failure of regenerative responses
Systemic implications	Loss of coordinated tissue regeneration and maintenance	Disrupted integration between immune system, stem cells, and niche	Decreased physiological adaptability and accelerated biological aging

Intercellular communication and tissue-level aging

Aging at the tissue level is significantly influenced by changes in intercellular communication that disrupt the coordination of immune function, regeneration, and maintenance of tissue homeostasis. Table 2 illustrates the relationship between changes in intercellular communication and aging at the tissue level through two main mechanisms: inflammation and stem cell exhaustion.

Inflammaging and immune dysregulation

Inflammaging describes a chronic, low-grade inflammatory state that develops gradually during aging and is a hallmark of physiological changes in the immune system (Saavedra *et al*., 2023). In contrast to the protective and transient acute inflammatory response, inflammaging is characterized by persistent but uncontrolled inflammatory activation, characterized by increased levels of proinflammatory mediators such as cytokines, chemokines, and acute-phase proteins (Karpuzoglu *et al*., 2025). This condition reflects a failure of inflammatory resolution mechanisms and contributes to the decline in tissue homeostasis in aging organisms (Lee *et al*., 2026).

Immune system dysregulation in aging involves changes in both innate and adaptive immune components (Gao *et al*., 2024). Immune cells exhibit decreased precision in responding to pathogens, accompanied by increased nonspecific basal activity (Netea *et al*., 2019). This condition is triggered in part by chronic antigen exposure, the accumulation of molecular damage, and changes in the tissue microenvironment (Yao *et al*., 2025). Consequently, the immune system shifts from a coordinated defense function to a state of constitutive activation, which actually amplifies systemic inflammation (Paludan *et al*., 2021).

The interaction between the immune system and somatic cells plays a key role in the development and maintenance of inflammation (Wang *et al*., 2024). Somatic cells experiencing stress, mitochondrial dysfunction, or senescence can release danger signals and inflammatory mediators that activate neighboring immune cells (Shi *et al*., 2025a). Conversely, dysregulated immune cells can affect somatic cell function through the secretion of proinflammatory cytokines, which impair tissue metabolism, differentiation, and regenerative capacity (Zaripova *et al*., 2023). This bidirectional interaction forms a feedback loop that maintains a chronic inflammatory state (Belkaid and Hand, 2014).

Within the framework of systems physiology, inflammation describes a disruption in cross-system communication involving immune, metabolic, and somatic networks (Bennett *et al*., 2018). Chronic low-grade inflammation not only affects a single organ but also impacts systemic function by increasing susceptibility to age-related diseases, including cardiometabolic disorders, neurodegeneration, and musculoskeletal decline (Santulli *et al*., 2025). Thus, inflammation reflects the consequences of a failure to integrate the immune response with the physiological needs of aging tissues, confirming that immune aging is a systemic process closely linked to the dynamics of cellular and tissue aging as a whole (Weyand and Goronzy, 2016).

Stem cell exhaustion and regenerative decline

Stem cells are crucial for tissue maintenance and repair due to their ability to self-renew and differentiate into functional cells (Wong *et al*., 2013). With aging, stem cell capacity gradually declines, a condition known as stem cell exhaustion, characterized by decreased proliferative potential, reduced differentiation capacity, and an increased tendency for cells to enter senescence or apoptosis (Ahmed *et al*., 2017). These changes directly limit the regenerative capacity of tissues and accelerate the decline in physiological organ function (Roger *et al*., 2021).

One of the primary causes of stem cell exhaustion is disruption of the stem cell niche, a specific microenvironment that provides structural, metabolic, and molecular signals to maintain stem cell function (Farahzadi *et al*., 2023). With aging, the niche undergoes changes in extracellular matrix composition, reduced vascular support, and increased inflammatory mediators (Xiao *et al*., 2023). These changes disrupt the signaling balance required to maintain proper stem cell quiescence and activation, leading to premature differentiation or failure of the regenerative response (Boaru *et al*., 2025).

In addition to being affected by niche changes, aging stem cells also experience an accumulation of intrinsic damage, such as genomic instability, mitochondrial dysfunction, and epigenetic changes (Rando *et al*., 2015). This damage reduces the stem cells' ability to maintain their identity and respond optimally to regenerative signals (Oh *et al*., 2014). As a result, although stem cells remain in number, their function declines, making tissue regeneration less efficient or uncoordinated (Signer and Morrison, 2013).

Within the framework of systems physiology, stem cell exhaustion and decreased regeneration reflect a failure of integration between stem cells, their niche, and the functional needs of the tissue (Velikic *et al*., 2024). This decline in regenerative capacity not only affects the tissue locally but also impacts the systemic balance through the accumulation of dysfunctional cells, increased inflammation, and reduced physiological adaptability of the organism (Saini, 2025). Thus, stem cell exhaustion provides a link between the molecular changes that occur during aging and the loss of tissue homeostasis, a hallmark of biological aging at the systemic level (Ren *et al*., 2017).

Systems-level integration of aging pathways

Aging occurs as a result of the integration of a network of interacting molecular pathways, in which metabolic signaling, stress responses, and longevity regulation are coordinated within a complex biological system. Figure 3 illustrates the systems-level integration of aging pathways, highlighting how interconnected molecular networks coordinate metabolic signaling, stress responses, and longevity-regulating mechanisms within a complex biological system.

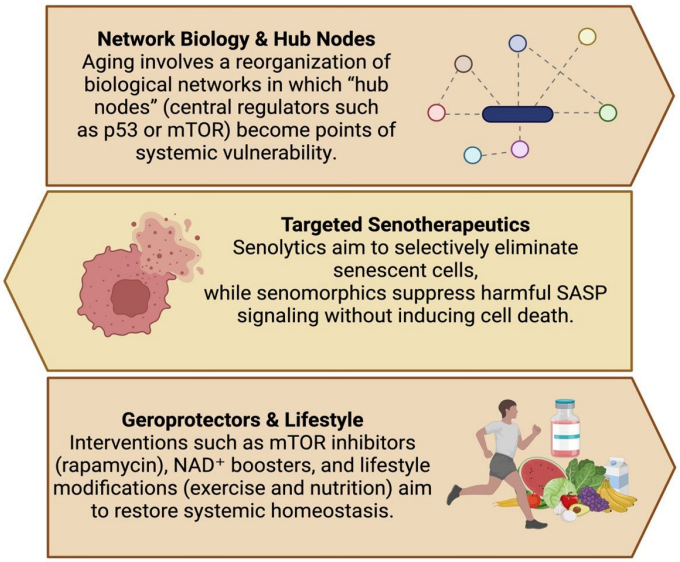

Figure 3. Systems-level integration and therapeutic targets

Network biology and aging

Biological aging cannot be explained solely by changes in a single gene or molecular pathway, but rather arises from the reorganization of complex regulatory networks (Zhou *et al*., 2018). Network biology offers an analytical framework for understanding aging as a systemic phenomenon, in which genes, proteins, and metabolites interact in dynamic net-

works that determine the stability and physiological adaptability of cells (Soltow *et al*., 2010). In this context, aging reflects a gradual shift in network architecture from a coordinated state to a more vulnerable and less responsive one (Deery *et al*., 2023).

Molecular network models of aging indicate that age-related changes tend to be focused on specific nodes and connections with important regulatory roles, rather than occurring randomly (Zhang *et al*., 2016). Pathways regulating stress responses, energy metabolism, DNA repair, and cell cycle control often experience changes in activity simultaneously, reflecting functional interconnections between these processes (Liu *et al*., 2025b). Network-based approaches allow for the identification of patterns of co-regulation and cross-pathway interactions that may be undetectable through conventional linear analysis (van Dam *et al*., 2018).

In biological networks, hub nodes are highly connected components that function as integrators of signals from multiple pathways (Mahapatra *et al*., 2021). With aging, hub nodes, such as transcription regulators, master kinases, or metabolic sensors, become critical points of vulnerability, as dysfunction in a single hub can affect multiple pathways simultaneously (Sharma and Ramanathan, 2020). This vulnerability explains why even small disruptions in key regulators can have widespread physiological impacts and accelerate the systemic aging process (Stojanovic *et al*., 2025).

Aging pathway convergence occurs when multiple molecular stresses such as DNA damage, mitochondrial dysfunction, and nutrient deregulation converge at the same network node, or module (Wei *et al*., 2025). These convergence points act as hubs between hallmarks of aging, thereby amplifying the cumulative effects of aging (Chistiakov *et al*., 2014). From a systems physiology perspective, understanding hub nodes and pathway convergence is crucial because it demonstrates that aging is not simply the accumulation of isolated damage but rather the result of a breakdown in coordination within regulatory networks that support physiological functions at multiple biological levels (Voicu *et al*., 2025).

Crosstalk between metabolism, stress response, and longevity

Cellular metabolism and stress response are two key regulatory systems intertwined in determining the survival and lifespan of organisms (Özbey *et al*., 2021). Metabolic pathways not only provide energy and materials for biosynthesis but also serve as internal sensors that translate nutrient status into physiological decisions for cells (Yuan *et al*., 2013). With aging, the integration between metabolic signals and stress responses changes, affecting the balance between protective adaptive mechanisms and the accumulation of cellular damage (Haigis and Yankner, 2010).

Metabolic signals, including glucose and amino acid availability, and cellular energy status, interact directly with stress response pathways to regulate gene expression, enzyme activity, and organelle dynamics (Carthew, 2021). Nutrient-sensing pathways—such as insulin/IGF-1, mTOR, AMPK, and sirtuins—serve as a link between metabolism and cellular protective mechanisms (Pignatti *et al*., 2020). Activation of anabolic pathways when nutrients are abundant promotes growth and proliferation, but simultaneously suppresses stress responses such as autophagy, DNA repair, and protein quality control (Galluzzi *et al*., 2014). Conversely, under conditions of metabolic stress or energy deficit, cells shift their focus to maintenance and resilience by activating pathways that increase metabolic efficiency and protect against damage (Liu *et al*., 2025b).

The balance between cell growth and maintenance is a fundamental principle in the biology of aging (Gasser and le Coutre, 2013). Excessive resource utilization for growth and reproduction tends to reduce allocation to long-term repair and protective mechanisms (English and Bonsall, 2019). With aging, this imbalance is often exacerbated by prolonged activation of growth signals and decreased sensitivity to stress, accelerating the accumulation of molecular damage (Polsky *et al*., 2022). This explains why interventions that suppress anabolic pathways or enhance adaptive stress responses are often associated with lifespan extension in various model organisms (Soo *et al*., 2023).

From a systems physiology perspective, the interactions between metabolism, stress response, and longevity are not linear, but rather are shaped by dynamic, context-dependent regulatory networks (van Beek *et al*., 2016). Small changes in one element of the network can shift the balance of the entire system, thus having far-reaching impacts on the function of the tissue and the organism as a whole (Chen *et al*., 2025b). Understanding this integration and trade-offs emphasizes that aging and longevity are determined by the ability of biological systems to regulate resource allocation between growth, maintenance, and adaptation to stress throughout the life cycle.

Emerging technologies in systems aging research

The development of high-resolution technologies and advanced computational approaches has expanded the understanding of aging by enabling integrated analyses of biological dynamics across scales and time. Table 3 summarizes the cutting-edge technologies supporting systems physiology approaches in aging research.

Multi-omics approaches

Multi-omics approaches have become a crucial cornerstone in aging research because they enable comprehensive mapping of biological

Table 3. New technologies in aging research based on systems physiology.

Technological approach	Level of analysis	Key information generated	Contribution to understanding systemic aging
Genomics	DNA and genome structure	Genetic variation, somatic mutations, genomic instability	Identification of genetic vulnerabilities and limits of cellular resilience to aging stress
Transcriptomics	Gene expression regulation	Gene expression patterns related to inflammation, stress, and cellular maintenance	Depicts dynamic cellular responses to aging and environmental cues
Proteomics	Proteins and post-translational modifications	Proteostasis disruption and altered protein interaction networks	Identifies functional dysfunctions not always reflected at the transcriptional level
Metabolomics	Metabolites and bioenergetic status	Mitochondrial dysfunction, redox imbalance	Direct link between molecular changes and physiological phenotype
Single-cell biology	Individual cell resolution	Cellular heterogeneity and aging trajectories	Reveals intercellular variation and dysfunctional subpopulations within tissues
Spatial biology	Tissue architecture and cell location	Spatial distribution of senescent cells and paracrine signals	Explains how local dysfunction spreads to broader tissue disruption
Computational modeling	Biological system dynamics	Simulation of aging trajectories and prediction of functional changes	Integrates multi-scale data to understand aging as a dynamic process
Artificial intelligence	Multi-dimensional data analysis	Pattern recognition, biomarkers, and intervention targets	Identification of key nodes and systems-based intervention strategies

changes at multiple levels of molecular organization (Ruden, 2025). Unlike single analyses that focus on only one regulatory layer, multi-omics strategies combine genomic, transcriptomic, proteomic, and metabolomic data to comprehensively understand the dynamics of biological systems (Yetgin, 2025). This approach is particularly useful in the study of aging, given that the aging process arises from complex interactions between molecular pathways that develop in a gradual and context-dependent manner (Nourazarain and Vaziri, 2025).

Genomics provides fundamental insights into genetic variation, genome instability, and the structural changes in DNA that accumulate with aging (López-Gil *et al*., 2023). Analyses in this area enable the detection of somatic mutations, changes in gene copy number, and genetic vulnerabilities that affect DNA repair capacity and cell resistance to stress (Vijg and Suh, 2013). However, genomic data is relatively static and does not fully reflect functional changes throughout life, requiring combination with other regulatory layers for a more comprehensive understanding (Rahnasto, 2023).

Transcriptomics maps changes in gene expression that reflect how cells respond to stress, metabolic changes, and environmental signals during aging (Tower *et al*., 2022). Age-related shifts in transcription patterns often indicate increased activity of inflammatory pathways, decreased expression of genes that maintain cell function, and increased intercellular heterogeneity in aging tissues (Stegeman and Weake, 2017). Transcriptomics data provide a dynamic view of how genetic information translates into biological responses in the context of aging (Perez-Gomez *et al*., 2020).

Proteomics deepens this understanding by analyzing the levels and modifications of proteins that directly regulate cellular function (Al-Amrani *et al*., 2021). In aging, changes in the proteome reflect impaired proteostasis, uncontrolled post-translational modifications, and altered protein interactions within regulatory networks (Morimoto and Cuervo, 2014). Through proteomics, researchers can identify dysfunctional functional nodes, even though changes at the transcriptional level are not always visible (Huang and Fraenkel, 2012).

Metabolomics represents the layer closest to the physiological phenotype, as it monitors changes in metabolite flux and the bioenergetic state of cells (Yang *et al*., 2025a). Aging-related metabolomic profiles reflect mitochondrial dysfunction, redox imbalance, and shifts in energy substrate utilization (Zhang *et al*., 2025). By combining metabolomic data with other omics layers, researchers can explore how changes in molecular regulation translate into functional impacts at the tissue and systems levels of the organism (Wörheide *et al*., 2021).

From a systems physiology perspective, the primary advantage of the multi-omics approach lies in its ability to uncover cross-scale relationships between genetic information, gene expression regulation, protein function, and metabolic output (Yetgin, 2025). The integration of these multiple layers allows for more precise modeling of aging networks and the identification of points of convergence that can potentially be targeted for intervention (Kaur *et al*., 2025). Thus, multi-omics not only broadens our understanding of the molecular aspects of aging but also elucidates how these changes are coordinated within the context of systemic physiology.

Single-cell and spatial biology

The development of single-cell technology and spatial biology has shifted the understanding of aging from a mere average phenomenon of cell populations to a highly heterogeneous and context-dependent process (Tam and Bushnell, 2024). Conventional bulk-based analyses often obscure variations between cells, thus failing to capture distinct aging dynamics across cell subpopulations within the same tissue (Yang *et al*., 2025b). With this high resolution, specific cell changes underlying tissue function decline during aging can be more accurately identified (Rong and Zhou, 2025).

Single-cell analyses demonstrate that aging does not occur uniformly, even among cells of the same type and origin (Uyar *et al*., 2020). With aging, tissues exhibit increasing heterogeneity at the transcriptomic, epigenetic, and metabolic levels, reflecting differences in cellular adaptability (Palmer *et al*., 2021). Some cells maintain relatively stable protective and functional programs, while other subpopulations undergo premature dysfunction, senescence, or phenotypic changes (Zhu *et al*., 2021). This variability contributes to imbalanced tissue function and accelerates the loss of physiological homeostasis (Li *et al*., 2025).

The single-cell approach also allows mapping of cellular aging trajectories, including the gradual transition from a functional state to senescence or dysfunctional differentiation (Mansfield *et al*., 2024). This trajectory analysis reveals that aging typically involves progressive, rather than abrupt, changes in gene regulation and is influenced by interactions with the microenvironment (Tao *et al*., 2024). Thus, cellular aging can be understood as a dynamic process determined by regulatory decisions at the individual cell level (Godoy and Hao, 2025).

Meanwhile, spatial biology adds a contextual dimension by preserving information about cell position within a tissue (Lee *et al*., 2025). This approach demonstrates that age-related changes are strongly influenced by tissue structure and cell-cell interactions (Pang *et al*., 2025). Cells undergoing senescence or metabolic dysfunction tend to congregate in specific niches, forming microenvironments that influence neighboring cells through paracrine signals (Zhang *et al*., 2023a). This spatial distribu-

Table 4. Translational implications and therapeutic strategies based on systems physiology in aging.

Therapeutic approach	Primary target	Key mechanism	Systemic physiological impact
Senolytics	Senescent cells	Selective elimination of SASP-producing senescent cells	Reduction of chronic inflammation and improvement of tissue function
Senomorphics	Senescent cell phenotype	Suppression of SASP and pathological paracrine signaling	Stabilization of tissue microenvironment without cell loss
Geroprotectors (mTOR modulators)	Nutrient-sensing pathways	Partial inhibition of mTOR and regulation of anabolism	Enhanced metabolic efficiency and stress resilience
NAD^+–Sirtuin modulators	Energy metabolism and epigenetics	Increase NAD^+ levels and activation of sirtuins	Restoration of mitochondrial function and DNA repair
Nutritional interventions	Systemic metabolic sensors	Regulation of energy intake and macronutrient composition	Optimization of metabolism and stress adaptation
Lifestyle modifications	Mitochondrial and immune function	Physical activity and stress management	Improved inter-organ communication and functional capacity
Personalized approaches	Individual biological variability	Tailoring interventions based on molecular profiles	More effective and sustainable therapeutic responses
Systems-based strategies	Multiple regulatory networks	Integration of nutrition, pharmacology, and lifestyle	Restoration of physiological balance and systemic homeostasis

tion pattern explains how dysfunction at the local level can expand into disruptions that affect the entire tissue (Gurkar *et al*., 2023).

From a systems physiology perspective, the integration of single-cell and spatial biology provides deeper insights into how cellular heterogeneity influences aging at the systemic level (Shi *et al*., 2025b). This approach emphasizes that aging is influenced not only by internal molecular changes in cells but also by the location of cells within tissues and their interactions (Cohn *et al*., 2023). Thus, high-resolution technologies at the single-cell and spatial levels are key to linking molecular changes to tissue and organ dysfunction in the aging process of the organism as a whole (Sun *et al*., 2025).

Computational modeling and artificial intelligence

The complexity of biological aging, which arises from the nonlinear interactions between molecular, cellular, and physiological pathways, makes computational approaches crucial in modern aging research (Mc Auley *et al*., 2017). Computational modeling and artificial intelligence (AI) enable the integration of large, multidimensional data sets to identify hidden patterns that are difficult to detect through traditional experimental analysis (Fahim *et al*., 2025). Within the framework of systems physiology, these approaches serve as a bridge between molecular information and the dynamics of systemic function throughout an organism's lifespan (Neoaz and Amin, 2025).

Computational models are widely used to predict aging trajectories by mimicking biological changes that occur over time (Srour *et al*., 2025). By leveraging longitudinal and multi-omics data, these models can map the trajectory of progressive cell and tissue decline, including the transition to senescence or metabolic dysfunction (Li *et al*., 2026). Machine learning-based approaches enable the discovery of early markers that are predictive of accelerated aging, while also providing insight into interindividual variations in the rate and pattern of aging (Levy *et al*., 2025).

In addition to prediction, AI also plays a crucial role in identifying intervention targets that have the potential to modulate the aging process (Mahbub *et al*., 2026). Algorithm-based network analysis enables the identification of critical nodes and points of convergence of regulatory pathways that have a greater systemic impact than a single target (Erbe *et al*., 2022). This approach is particularly relevant in the context of aging, where interventions on a single molecule often have limited effects due to redundancy and biological compensatory mechanisms (Cohen *et al*., 2022). By modeling the system's response to controlled perturbations, computational strategies can prioritize targets that have the most significant physiological impact (Gavriilidis *et al*., 2024).

Furthermore, combining AI with experimental data enables in silico evaluation of potential interventions, including genetic manipulation, metabolic modulation, and pharmacological therapies (Alharthi, 2025). These simulations can predict the long-term impact of interventions on tissue homeostasis and organ function, while also anticipating side effects resulting from disruptions to the system's balance (Sharma and Chen, 2025). Thus, computational modeling supports the design of more rational, systemic anti-aging strategies (Ma and Gurkan-Cavusoglu, 2024).

From a systems physiology perspective, computational modeling and AI are not simply tools for analyzing data; they also provide a conceptual framework for understanding aging as a coordinated, dynamic process (Kalu *et al*., 2025). This approach enhances the ability to link molecular changes to physiological outcomes and offers opportunities for developing precision interventions that account for the complexity of biological systems as a whole (Sul *et al*., 2025).

Translational implications and therapeutic perspectives

Understanding the molecular mechanisms of aging from a systems physiology perspective opens up significant translational opportunities for the development of therapeutic strategies that target fundamental aging processes in an integrated and contextual manner. Table 4 summarizes the translational implications of a systems physiology-based understanding of aging, highlighting therapeutic strategies that target fundamental aging mechanisms in an integrated manner.

Geroprotectors and senotherapeutics

Therapeutic efforts to address aging are increasingly shifting from symptomatic strategies to approaches that target the fundamental mechanisms of aging (Sanada *et al*., 2025). Within this framework, geroprotective and senescent therapies have emerged as a class of interventions designed to slow the rate of biological aging or mitigate the effects of senescent cells on tissue function (Mandelblatt *et al*., 2025). These strategies are based on the understanding that aging is not simply the result of accumulated damage but rather a regulatory process that can be modified through specific molecular pathways (Gaspar-Silva *et al*., 2023).

Senotherapy encompasses two main approaches: senolytic and senomorphic. Senolytics are designed to eliminate senescent cells that accumulate with aging (Saliev and Singh, 2025). Although these cells cease dividing, they remain metabolically active and often produce a SASP, which is pro-inflammatory and detrimental to the tissue environment (Luca *et al*., 2025). Selective removal of senescent cells has been shown to improve tissue function and stabilize systemic homeostasis in various experimental models, confirming that senescent cell accumulation is a key factor in physiological aging (Roger *et al*., 2021).

In contrast, senescent cells are not targeted at eliminating senescent cells, but rather at altering their phenotype by suppressing the SASP and its paracrine effects (Birch and Gil, 2020). This strategy is useful in tissues with limited regenerative capacity, where cell removal could compromise structural function (Song *et al*., 2020). By stabilizing the tissue microenvironment, senescent cells help maintain physiological function without significantly compromising cell integrity (Kumari and Jat, 2021).

In addition to directly targeting senescent cells, many geroprotectors act through key regulatory pathways that integrate metabolism, stress response, and longevity (Alum *et al*., 2025). The mTOR pathway plays a key role in regulating cell growth and nutrient utilization, and its overactivity is associated with accelerated aging (Raghuvanshi *et al*., 2025). Partial inhibition of mTOR has been shown to increase metabolic efficiency and cell resistance to stress, emphasizing the importance of maintaining a balance between anabolic processes and cellular maintenance mechanisms during aging (Mannick and Lamming, 2023).

NAD^+ metabolism and sirtuin activity are also key focuses in geroprotective strategies (Covarrubias *et al*., 2021). The decline in NAD^+ levels that occurs with aging impacts mitochondrial function, DNA repair, and epigenetic regulation broadly (Yusri *et al*., 2025). Increasing NAD^+ availability can restore cellular adaptive capacity and improve coordination between metabolic pathways (Amjad *et al*., 2021). Meanwhile, sirtuins act as energy status sensors, linking metabolic signals with transcriptional regulation and genome stability, thus crucial for maintaining cellular homeostasis throughout the aging process (Houtkooper *et al*., 2012).

From a systems physiology perspective, the effectiveness of geroprotective and senotherapeutic agents depends not solely on a single molecular target but also on their influence on broader regulatory networks (Saliev and Singh, 2025). Successful interventions are those that can redirect a biological system from a dysfunctional state to a new, more adaptive balance (Maner and Kenrick, 2010). Therefore, the development of anti-aging therapies requires a comprehensive understanding of the interactions between molecular pathways, network dynamics, and their impact on the physiological function of the organism as a whole.

Systems-based intervention strategies

Systems-based intervention approaches view aging as a multifactori-

al process that cannot be effectively reversed through a single intervention (Tosato *et al*., 2007). Aging involves complex interactions between metabolism, inflammation, hormonal regulation, and tissue function, making holistic therapeutic strategies increasingly important (Zhang *et al*., 2023b). Systems-based intervention strategies aim to restore physiological balance by simultaneously and coordinately targeting multiple regulatory pathways (Maguire, 2019).

The combination of nutrition, pharmacological therapy, and lifestyle changes is a clear example of the application of a systems-based approach to managing aging (Kalache *et al*., 2019). Nutritional interventions, such as regulating calorie intake and macronutrient composition, influence nutrient-sensing pathways that regulate metabolism and cellular stress resistance (Solon-Biet *et al*., 2015). Conversely, certain medications can enhance or adapt physiological responses triggered by nutritional changes, for example by modulating metabolic, inflammatory, or proteostatic pathways (Niederberger and Parnham, 2021). The integration of these two strategies produces a more consistent synergistic effect than either strategy alone.

Lifestyle changes, such as regular exercise and stress management, directly impact mitochondrial function, metabolic sensitivity, and immune system regulation (Bhatti *et al*., 2017). Consistent physical activity not only improves tissue functional capacity but also influences interorgan communication through the systemic release of signaling molecules (Walzik *et al*., 2024). From a systems physiology perspective, lifestyle impacts are understood as a comprehensive modulation capable of coordinating adaptive responses at multiple levels of biological organization (Parker *et al*., 2022).

Advances in personalized aging medicine further emphasize the importance of a systems-based approach that tailors interventions to each individual's biological characteristics (Edvardsson and Heenkenda, 2025). Differences in genetics, epigenetic status, metabolic profiles, and environmental factors contribute to variations in response to anti-aging strategies (Ciaglia *et al*., 2025). With a personalized approach, the most appropriate combination of interventions can be selected to maintain physiological function and slow the rate of aging on an individual basis (Tenchov *et al*., 2024b).

From a systems physiology perspective, the effectiveness of systems-based interventions is determined by the ability to understand and predict the biological responses that arise from the interactions of the intervention's various components (Alfonso-González *et al*., 2025). This approach emphasizes the need for dynamic adaptation and continuous monitoring of physiological conditions, allowing for gradual adjustment of anti-aging strategies (Tenchov *et al*., 2024b). Thus, systems-based intervention strategies provide a promising conceptual framework for designing more efficient, sustainable, and clinically applicable anti-aging therapies.

Challenges and future directions

Despite significant progress in understanding the molecular mechanisms of aging through a systems physiology approach, a number of conceptual and methodological challenges still limit the application of this knowledge to a more comprehensive biological understanding and clinical implementation (Li *et al*., 2024). These challenges reflect the complexity of aging as a multidimensional biological process involving interactions across scales and between systems (Cohen *et al*., 2020).

One major challenge is the biological complexity of aging itself, which is difficult to fully capture with experimental models (Borrás, 2021). While in vitro models and model organisms have provided important insights into aging pathways, they often fail to reflect the systemic interactions between tissues and organs that occur in intact organisms (Sen *et al*., 2016). Furthermore, interspecies differences in metabolic regulation, stress responses, and senescence dynamics limit the broad applicability of these findings (Kwon *et al*., 2019). Therefore, the development of more physiological models—such as complex organoids, organs-on-a-chip, and animal models with high translational validity—is essential to bridge the gap between molecular mechanisms and systemic function (Han *et al*., 2024).

Validating findings from systems biology approaches in humans remains a significant challenge. Many pathways and targets discovered through multi-omics strategies and computational modeling have not yet been fully demonstrated to be relevant in the highly heterogeneous context of human aging (Pinu *et al*., 2019). Genetic, environmental, and lifestyle differences result in a broad spectrum of biological responses, making it difficult to draw general conclusions (Zi *et al*., 2023). Therefore, large-scale longitudinal studies combined with multi-level analyses are needed to ensure that the identified patterns and mechanisms truly reflect the human aging process and are not simply artifacts of experimental models or statistical analysis methods (Roberts *et al*., 2017).

Another important challenge is managing big data integration while standardizing methodology (Luna *et al*., 2014). Systems physiology approaches rely heavily on large-scale multi-omics, single-cell, and clinical data obtained from diverse platforms and protocols (Mohr *et al*., 2024). Differences in study design, measurement techniques, and analysis strategies often hinder the reproducibility and comparability of results across studies. Therefore, developing a standardized framework for data collection, processing, and integration is essential for the field to thrive (Chehelgerdi *et al*., 2023). Furthermore, increasing algorithm transparency and cross-validation of computational models will further strengthen the reliability of data-driven interpretations (Sweet *et al*., 2023).

Going forward, systems physiology-based aging research is expected to increasingly emphasize the integration of experiments, computational modeling, and clinical data (Kushner *et al*., 2025). A multidisciplinary approach combining molecular biology, physiology, data science, and precision medicine has the potential to provide a more comprehensive understanding of the aging process (Chiti *et al*., 2025). By addressing these challenges, systems physiology can serve as a strategic framework for identifying key mechanisms of aging and guiding the development of more effective and physiologically relevant interventions (Cohen *et al*., 2020).

Conclusion

Cellular aging results from the complex interaction of multiple molecular mechanisms, including genomic instability, mitochondrial dysfunction, impaired proteostasis, metabolic deregulation, and the accumulation of senescent cells, which collectively degrade the function of physiological tissues and systems. These mechanisms do not operate in isolation but are interconnected within a dynamic and biologically contextual regulatory network.

A systems physiology approach offers the significant advantage of viewing aging as an emergent phenomenon across scales, from the molecular to the organismal. By integrating multilevel data and emphasizing interactions between biological systems, this approach transcends the limitations of reductionist analysis and offers a more physiologically relevant conceptual framework.

Going forward, aging research is predicted to increasingly focus on integrative and predictive strategies, combining experimental, computational, and clinical methods. A systems-based perspective can not only deepen our understanding of aging mechanisms but also open up opportunities for the development of more precise and effective interventions to maintain health throughout life.

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Conflict of interest

The authors have declared no conflict of interest.

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